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# **Does allergy explain why some children have severe asthma?**

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**Abbreviations**

SA severe asthma

STRA severe therapy-resistant asthma

ICS inhaled corticosteroid

AR allergic rhinitis

SPT skin prick test

sIgE specific immunoglobulin E

WHO World Health Organisation

HDM house dust mite

SMART Symbicort maintenance and reliver regime

OR odds ratio

CI confidence interval

FA food allergy

SAFS severe asthma with fungal sensitisation

ABPA allergic bronchopulmonary aspergillosis

FENO fraction exhaled nitric oxide

HRV human rhinovirus

## Abstract

Asthma is a common disease in childhood with a minority of affected children having severe therapy-resistant asthma (STRA). Children with STRA can be differentiated from those with mild-moderate disease by greater allergic sensitisation, increased eosinophilic airway inflammation, increased airway remodelling, and reduced corticosteroid responsiveness. The aetiology of STRA in children is multifactorial but allergy seems to play a key role. Many children with asthma have co-existing allergic disease, and severe rhinitis seems to be an important driver of STRA in children. Allergies to foods, moulds, pollen and pets have also been associated with severe asthma exacerbations. Identifying allergens that are driving asthma symptoms in children with STRA may provide additional strategies for improving their disease control. Avoidance strategies may be possible. Additional monoclonal antibody therapy with Omalizumab or Mepolizumab may be helpful in children with clinically important polysensitisation.

## Introduction

Asthma is the most common chronic lung disease of childhood and affects approximately 25% of children in the United Kingdom.1 Fortunately, most children with asthma achieve good symptom control with low-dose inhaled corticosteroid (ICS). Some children have asthma that is difficult to treat despite high doses of ICS and additional controller medications due modifiable factors, commonly poor adherence to ICS or persistent exposure to environmental triggers.2 These children with ‘difficult asthma’ account for up to 97% of referrals to paediatric asthma clinic and can achieve good symptom control if these modifiable factors are adequately addressed.3 However, 2-5% of children with asthma remain symptomatic despite addressing modifiable factors and treatment with high-dose ICS, long-acting β2-receptor agonists, leukotriene receptor antagonists and occasionally systemic corticosteroids.4-9 These children have ‘severe therapy-resistant asthma’ (STRA) (Box 1).10 Despite the low prevalence of STRA, it accounts for significant morbidity and almost 50% of total asthma-related expenditure.5,7,11

It is imperative that children with difficult asthma undergo thorough assessment to identify and address modifiable factors before undergoing invasive investigations and further escalation of potentially harmful treatments for STRA.12 This involves confirming the diagnosis of asthma by demonstrating variable and reversible airflow obstruction,13-15 ensuring adherence to treatment by checking general practitioner prescription records and that the appropriate inhalers are available on the home visit,2,16 and checking the child’s inhaler technique,17 It is also necessary to minimise exposure to environmental allergens where possible,2 avoid pollutants including cigarette smoke,13 and manage comorbidities including obesity,9 dysfunctional breathing and vocal cord dysfunction, allergic rhinitis and food allergy.18,19

Clinically, children with STRA are differentiated from those with mild-moderate disease by greater allergic sensitisation, increased eosinophilic airway inflammation, increased airway remodelling, reduced lung function and reduced corticosteroid responsiveness.2,20,21This is further complicated because children with STRA are themselves a heterogeneous group in terms of lung function, inflammation and allergic sensitisation, and different phenotypes of STRA are being recognised.2,20,22-25 Improving our understanding of the factors driving STRA may allow better targeting of therapy and potentially improve outcomes.26

## STRA and Allergy

Allergy is likely to be an important factor involved in STRA as children with more severe asthma are more atopic (have more allergic sensitisations), and tend to be exposed to higher levels of allergens to which they are sensitised when compared with children with mild asthma.13,27 Plus the greater the number of organ systems affected by allergy, the worse the prognosis of each of the allergic diseases (e.g. eczema, food allergy), and particularly asthma.28 It is plausible that persistent exposure to allergens, which may also manifest as rhinitis, eczema or food allergy, may drive airway inflammation and STRA. Reducing exposure to environmental allergens and anti-IgE therapy are both effective in managing STRA thereby supporting this hypothesis.14,18

In this review we examine the hypothesis that asthma is an allergic disease of the airways and propose that allergy is a key determinant of STRA (see online supplement for search strategy). The role of allergic co-morbidities and environmental allergen exposure in STRA will be the focus of this review. Diagnosing asthma in pre-school children that wheeze is challenging, so we do not consider this age group here.

**Box 1. Definitions of severe asthma in school age children**

Various definitions of severe asthma (SA) in this age group are used, including:

**‘Problematic severe asthma’** – asthma that remains poorly controlled despite high-dose inhaled steroids (≥ 800µg/day budesonide or equivalent), additional controller medication, and on stage 4/5 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network guideline.

**‘Difficult asthma’** –the subset of problematic SA which is poorly controlled due to: incorrect diagnosis, aggravating comorbidities, poor adherence to treatment, inadequate inhalation technique, persistent exposure to environmental allergens or pollutants, or adverse psychosocial factors, which may manifest as dysfunctional breathing or vocal cord dysfunction.13

**‘Severe therapy-resistant asthma’** –the small subset of patients that remain symptomatic despite management of the above factors. This term is reserved for patients with poor baseline asthma control or frequent severe exacerbations despite high intensity treatment, where alternative diagnoses have been excluded, co-morbidities treated, environmental triggers eliminated (where possible), and compliance optimised.10,13

The terms ‘difficult asthma’ and STRA (Box 1) are becoming more widely adopted in publications, allowing results to be compared and conclusions drawn. Unfortunately, the vague term ‘severe asthma’ is still used relatively indiscriminately in some publications to describe children with any features of more severe asthma based on: reported symptoms, treatment requirements, frequency of exacerbations, objective measures of airflow limitation or measures of inflammation. Given the apparent heterogeneity among patients with STRA, it is essential that we accurately classify and characterise these patients in order to draw accurate conclusions about factors implicated in the disease and effectiveness of interventions.

## STRA and allergic co-morbidities

#### Allergic Rhinitis

Allergic rhinitis (AR) involves allergen-driven inflammation of the upper airways, and affects approximately 80% of children with asthma, although it is often underdiagnosed and undertreated.18,29-33 Many studies in children have shown that AR, especially if severe and persistent, is associated with markers of more severe asthma, including increased night-time cough, increased beta-agonist and steroid use, more frequent episodes of wheeze limiting speech, more frequent hospitalisation and more missed school days.18,30,34-41 In a survey of 3066 Japanese children with asthma, severe AR was associated with uncontrolled asthma identified on the Childhood Asthma Control Test (Odds Ratio (OR) 3.88, 95% Confidence Interval (CI) 2.05-6.00), and there was a significant positive correlation between increasing AR severity and asthma severity (p<0.001).42

The ‘unified airway’ concept suggests that upper airway disease (AR) and lower airway disease (asthma) are both manifestations of the same IgE-dependent eosinophilic inflammatory process, being driven primarily by exposure to inhalant allergens.19,34,43 The association between AR and asthma severity could then be explained by the larger burden of inflammation seen when both conditions are present. It is also possible that the relationship between AR and asthma could be, at least in part, causal. One study confirmed that the association between AR and SA remained significant even after adjustment for total serum IgE and polysensitisation to aeroallergens, suggesting rhinitis may directly impact on asthma severity.30 Studies showing that provocation of nasal mucosa with allergen in patients with AR caused pulmonary symptoms and decreased airway function, and similarly segmental bronchial provocation triggered nasal inflammation, support the unified airway concept.34,44,45 AR may also be causally linked to asthma severity through impaired function of the upper airways, which includes filtering, warming and humidifying air before it reaches the lower airways.19,34,45-47 This idea is supported by findings of significantly impaired lung function in children with moderate-severe persistent rhinitis, compared to mild intermittent rhinitis, in children without overt asthma symptoms, which was independent of atopic status.48 Nasal obstruction due to AR necessitates mouth-breathing which may result in bronchial hyperreactivity due to cold dry air, and greater delivery of allergens to the lower airways.44,46 These mechanisms may underlie the relationship between AR and STRA.

The Royal College of Paediatrics and Child Health pathway for children with asthma or rhinitis recommends that a detailed assessment should be performed to detect the presence of the other condition.19 This should include an assessment of allergen triggers for nasal symptoms with skin prick test (SPT) or specific IgE (sIgE) testing to guide avoidance of these triggers.19 Where both conditions exist, ongoing management should address the upper and lower airways together.19 The recommended first-line treatment of moderate-severe persistent AR in children is intranasal corticosteroid, if necessary with oral second-generation non-sedating or intranasal antihistamines, and saline nasal washes.33,34,49,50 Oral leukotriene receptor antagonists may be considered where symptoms persist.33,49 Observational studies have suggested that intranasal corticosteroid use improves asthma control in children, consistent with clinical trials in adults, but no randomised controlled trials looking at the effects of treatment of AR on asthma control in children were identified.29,30,34,36,50 Anti-IgE monoclonal antibody, Omalizumab, improves nasal and bronchial symptoms in patients with AR and STRA.34 Specific immunotherapy to allergens including pollens and house dust mite (HDM) which trigger AR is generally contraindicated in children with STRA due to the potential for adverse effects, but has successfully treated AR in children with mild or no asthma.33,34

#### Eczema

Eczema affects 15-38% of children and usually precedes the onset of asthma.28,51-55 The filaggrin gene has been identified as important in eczema, with loss-of-function mutations being associated with skin barrier dysfunction and an increased incidence of asthma.51,53 In one birth cohort study, eczema with filaggrin loss-of-function mutations was associated with STRA and reduced lung function at puberty.22 We can speculate that ongoing exposure of eczematous skin to allergens may result in the development of polysensitisation, driving systemic allergic inflammation and worsening of asthma symptoms. Alternatively, the association between eczema and asthma may not be causal. Randomised controlled trials (eg ClinicalTrials.gov NCT02449850) of skin barrier agents are now ongoing and may provide more information in time.

#### Food allergy

Food allergy (FA) affects 2.5-4.2% of all children and 10% of children with asthma, and is associated with asthma severity, including more night-time symptoms, higher steroid requirements, more frequent asthma exacerbations and more hospital and intensive care admissions.18,54,56-58. In a prospective study of 174 children less than 36 months old sensitised to food and aeroallergens on SPT, follow-up 7-14 years later showed those with persistent food and aeroallergen sensitisation had much more severe asthma compared with those that had only aeroallergen sensitisation.56 In the National Cooperative Inner City Asthma Study, children aged 4-9 years with asthma and food sensitisation on sIgE testing had significantly higher rates of hospitalisation and required significantly more steroid medication than those not sensitised to food.59 A study by Roberts *et al.* found children with acute life-threatening asthma requiring ventilation were much more likely to have clinical FA than those attending the emergency department with non-life threatening exacerbations.60 Additionally, a study of 201 children with asthma found peanut and milk allergy were independently associated with hospitalisations for asthma exacerbations.61 In other studies multiple food allergies have been associated with STRA16,59,61

It is not clear whether the observed relationship between STRA and FA is due solely to a shared stronger atopic tendency, or whether a causal pathophysiological link is responsible.62 Several mechanisms have been proposed for a causal link. Firstly, some anaphylactic reactions to food may be misdiagnosed as acute exacerbations of asthma, especially where exercise is a co-factor for severe reactions to food.57,60,62,63 In a retrospective analysis of the records of 73 children admitted to intensive care with asthma, a diagnosis of anaphylaxis was considered possible in 17.8% and highly likely in 4.1%.63 Secondly, ingestion of food allergens in some children may cause a less severe allergic reaction manifesting primarily as worsening of asthma symptoms. Whilst FA manifesting as asthma is thought to be rare, it has been reported that ingestion of food allergens in children with asthma can trigger asthma symptoms up to 30% of the time.54,57 Thirdly, it has been proposed that chronic inhalation of aerosolised food allergens may increase asthma severity.60,62 Occupational asthma in adults is widely recognised, with Baker’s asthma being most commonly due to inhalation of airborne flour in those with wheat allergy, though milk powder, egg, carob bean and soya flour have also been implicated.60,62 The pathophysiology and histological findings of occupational and allergic asthma in adults are similar, but studies in children were not identified.62

Despite the uncertain nature of the relationship between STRA and FA, having both conditions is a risk factor for increased morbidity and mortality, so accurate diagnosis of FA in children with STRA is essential and both conditions should be managed optimally.54,64 Referral to a dietician for education on food avoidance, reading of food labels, appropriate food substitutions, and monitoring of growth is recommended. Regular patient and parent education regarding appropriate treatment of allergic reactions including autoinjector use is vital, since many fatal cases could have been avoided by more prompt adrenaline administration.65 Optimal asthma management and compliance with treatment is needed to reduce the risk of fatal food-related anaphylaxis associated with accidental exposure.65

## STRA and environmental aeroallergens

Common aeroallergens include HDM (Dermatophagoides pteronyssinus and farinae), cat, dog and mouse epithelium, grass, tree and weed pollens, and moulds (Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum and others).66-68 In warmer climates cockroach, rice dust, mosquito and housefly sensitisation are also common.69

#### House Dust Mite

In the UK 65% of children with asthma are sensitised to HDM, ,70 and exposure to HDM results in asthma symptoms.71,72 In a randomised study of 82 children with asthma, there was a positive linear association between increasing asthma severity and response to chemical HDM control measures, suggesting that HDM exposure is important in driving asthma symptoms.73 A study of 546 inner-city adolescents with moderate-severe asthma found that higher HDM levels correlated with reduced lung function, higher airway inflammation and a greater risk of asthma exacerbation and hospitalisation.74

The management of children with asthma who are HDM sensitised involves attempts to minimise exposure to HDM in the home, pharmacotherapy to reduce the allergic response, and occasionally immunotherapy to induce tolerance and modify the disease process if asthma is not severe.67,71,75 Not all methods of reducing exposure to HDM have been demonstrated to work.76,77 However, a double-blind randomised controlled trial of mite-impermeable or placebo bedding covers used for 12 months in children sensitised to HDM, after a recent emergency hospital attendance for asthma, showed mite-impermeable covers halved the risk of emergency hospital attendance.70 In this study there was no reduction in the frequency of prednisolone use for exacerbations, but given the relatively low cost of the intervention and reduction in severe exacerbations requiring hospitalisation, mite-impermeable covers should be recommended for children with asthma and HDM sensitisation.

#### Pets

Allergy to cats and/or dogs is associated with increased bronchial hyper-responsiveness and airway inflammation, and is considered to be a risk factor for ongoing asthma morbidity.78-80 In children sensitised to their pet, pet allergen levels in house dust samples have been associated with asthma severity.81 In a study of 963 adolescents in Sweden, there was a highly significant positive relationship between sIgE titres to dog or cat allergens and asthma severity, measured by frequency of asthma exacerbations and medication use.82 In a study comparing children with severe and controlled asthma, the frequency of sensitisation to cat, dog and horse on SPT was similar between the groups but the levels of animal sIgE were significantly higher in the severe group, and they were more likely to be triple sensitised to the three animals.79 Polysensitisation to animals has been reported elsewhere to be associated with increased asthma severity in children.83

It is increasingly being recognised that pet allergens are readily transferred and exposure is ubiquitous in homes, schools and indoor public spaces.34,67,79,82 A study of 831 homes in the United States found cat and dog allergens in dust samples from >90% of homes, despite only 32% of homes having a dog and 24% having a cat.81 In the Swedish study, 50% of the adolescents with persistent asthma sensitised to cat or dog lived in a home with no animals, and 85% of those with asthma sensitised to cat had no cat at home.82Even small amounts of cat allergen on the clothes of classmates at school is sufficient to cause asthma deterioration in some children.14 Therefore sensitisation to cat and/or dog may also be contributing to worse asthma control in children from pet-free homes. These studies suggest pet exposure in sensitised children may be a driver of STRA, and all children with STRA, regardless of presence or absence of pets in the home, should be routinely tested for sensitisation to cats and dogs.79,84

Judging the impact that pet exposure has on a child’s asthma is very difficult as it is impossible to entirely eliminate pet allergen exposure, and an improvement in asthma symptoms on removing the child from the home with the pet is typically only seen after 2-3 weeks.72 Also, when pets have been in the household for a long time, early phase histamine mediated immediate symptoms of itch may be abolished although late phase asthma one persist; so caregivers may not recognise the impact on their child’s asthma and so may under-report symptoms. Measures that can effectively reduce pet allergen load, including high-efficiency vacuum cleaners and air filtration systems, have been shown to improve asthma control in sensitised children.80 In a study of adults with pet allergy and asthma, those that removed the pets from their home required less medication and had less bronchial hyper-responsiveness at follow-up compared to those that kept their pets.81 Similar studies in children were not found. We know that many people continue to live with a pet despite being allergic and removal of the pet from the household can have a dramatic psychological impact on a child.79,81 The lack of published evidence makes it difficult to insist families remove household pets, but for children with STRA and significant sensitisation on SPT and sIgE it would seem sensible to recommend re-homing the pet, at least for a trial period.

Several studies have investigated whether early regular exposure to pets in the home could reduce allergic sensitisation and asthma development in children.82 Results suggest being raised in a home with a cat does not increase the risk of sensitisation or asthma development, but no benefit in terms of developing tolerance to cats/dogs has been consistently demonstrated.85,86 For now advice should not be given to avoid or specifically acquire pets for primary prevention of asthma or pet allergies.85

Increasingly, the impact of exposure to pests particularly in low socio-economic areas on asthma severity in children is being understood. Mouse allergen is common in inner-city homes and schools, and high allergen load is associated with significant increased hospital presentations, reduced spirometry and bronchodilator reversibility, increased baseline asthma treatment, and increased Composite Asthma Severity Index (CASI).67,87,88 Similarly, cockroach exposure is common in inner-city homes in the United States and some areas of Europe and has been associated with asthma severity,89,90 Successful reduction in cockroach exposure using insecticidal bait in the homes of children with moderate-severe asthma was associated with a significant reduction in frequency of asthma symptoms, healthcare utilisation and missed school days due to asthma symptoms.91 In children with STRA, investigation to detect sensitisation and level of exposure to pests should be considered, particularly in low socio-economic areas, and exposure minimised through pest management.

#### Moulds

Mould spores are widespread in indoor and outdoor environments and increased levels have been associated with increased asthma symptoms and hospital admissions for asthma.67,68,92,93Sensitisation to one or more mould in children has been associated with severe asthma (defined by GINA classification), more frequent asthma exacerbations, increased admissions to intensive care, and increased use of maintenance oral steroids.24,94,95 Frequency of sensitisation and degree of skin-test positivity to *Alternaria* has been strongly linked to asthma severity, and exposure in those sensitised is associated with more frequent severe and life-threatening episodes of asthma.66,95,96 A study of 566 children with asthma in South Korea found those sensitised to mould compared with those sensitised to other aeroallergens but not mould had significantly lower lung function and increased airway hyper-responsiveness.97 There was no difference between the two groups in terms of incidence of rhinitis or eczema, FENO or blood oesinophil levels, suggesting the relationship between fungal sensitisation and STRA is not merely due to increased atopic tendency. A similar study showed those sensitised to moulds compared with those sensitised to other aeroallergens but not moulds had a significantly lower FEV1 and were more likely to have STRA, suggesting moulds may play a greater role in STRA than other aeroallergens.98

However, this strong association between fungal sensitisation and STRA is not demonstrated in all studies.99 The Melbourne Air Pollen Children and Adolescent Study investigated 644 children hospitalised for asthma and found exposure to ambient levels of Alternaria and other common fungal spores was significantly associated with hospitalisations for asthma.100 At the time of hospitalisation 69% were infected with human rhinovirus (HRV), but the risk associated with ambient mould levels remained after controlling for HRV infection, suggesting moulds and viruses act synergistically to increase exacerbation risk. This risk was also independent of ambient pollen and pollution levels, and the effects were seen up to 3 days after exposure. The increased risk of hospitalisation was seen in children with asthma with and without fungal sensitisation measured by SPT, and while the risk appeared higher in those sensitised, this did not reach statistical significance. In an international cross-sectional study of 46,051 children, asthma symptoms and exposure to damp spots or moulds in the house was assessed by parental questionnaire, and exposure to damp or moulds was associated with greater severity of wheeze, but not bronchial hyper-responsiveness, in children regardless of atopic status.101 Other studies have similarly found that exposure to moulds is associated with asthma severity in atopic and non-atopic children.102

The pathophysiology underlying the observed link between STRA and moulds is not clear but several mechanisms have been proposed. Firstly, it has been assumed that an inflammatory response occurs in the airways of sensitised children in response to exposure to allergenic components of environmental fungi.103 Secondly, long-term colonisation or infection of the airways with allergenic fungi could provide a persistent source of allergen exposure and trigger pro-inflammatory host defence mechanisms.95,97,103,104 Severe asthma with fungal sensitisation (termed SAFS) may represent a discrete phenotype of STRA, with properties similar to allergic bronchopulmonary aspergillosis (ABPA) in adults, and possible improvement with antifungal therapies.24,103-105 SAFS is typically associated with worse inflammation than other phenotypes of STRA despite more asthma treatment.9 It has even been reported that chronic fungal infection of the skin and nails can exacerbate asthma, with improvement in asthma symptoms and lung function on treatment of the infection.24 Thirdly, it has been proposed that some fungal antigens can trigger autoimmune reactions, when an immune response targeting a fungal protein also targets the closely related human counterparts, potentially exacerbating airway inflammation.24 Finally, moulds in indoor environments, including bedding, are known to release volatile components that may irritate the respiratory mucosa and increase asthma severity independently of allergic mechanisms.24

There are several possible explanations for the inconsistent relationship between STRA and fungal sensitisation. Fungal spores are ubiquitous in indoor and outdoor environments but levels vary with geographical area and weather/climate conditions, so it can be difficult to establish a link between exposure and asthma symptoms.68,95,100 The link is also complicated by a degree of cross-reactivity between the different fungal species and the fact that many children are polysensitised to various moulds and pollens with overlapping seasons.66,100 Accurately detecting fungal sensitisation is complicated by variable use of SPT and sIgE in different studies and a lack of standardised reagents for SPT. Many studies have not considered degree of sensitisation or quantified exposure to moulds, and have relatively small sample sizes.100 Finally, exposure to moulds may drive STRA in some children through a combination of allergic and non-allergic mechanisms outlined above. More research is needed to understand which of these mechanisms are responsible for the relationship between STRA and moulds in children.

In children with STRA it is important to assess for mould sensitisation and exposure so appropriate avoidance measures can be taken. A combination of SPT and sIgE quantification are recommended as together they can accurately predict clinical reactivity.24 Management of SAFS can be difficult as spore concentrations can be unpredictable and exposure difficult to avoid.68 Advice regarding potential risk situations such as thunderstorms and handling mouldy vegetation should be given to mitigate the effects of outdoor exposures.66 Evidence for a potential benefit of antifungal therapy in SAFS is very limited,24 and techniques for fungal culture from sputum and bronchoalveolar lavage have low sensitivity for detecting infection.98 Whilst case-reports are positive, randomised controlled trials are needed to understand the role of antifungals in SAFS.

#### Pollens

Pollen is known to be a strong trigger for seasonal AR and conjunctivitis and has been reported to trigger asthma exacerbations in sensitised children.34 In a study in Atlanta, ambient grass and tree pollen levels contributed to asthma morbidity in children, with a significant 10-15% increase in emergency department attendances for asthma on the days with the highest pollen concentrations.106 Other studies have shown similar results.107 A recent meta-analysis showed small increases in grass pollen levels (of 10 grass pollen grains per cubic meter) are associated with a significant increase of in mean number of asthma exacerbations in children presenting to the emergency department.108 Pollen levels can vary considerably throughout the year, with levels up to 100 grains/m³ resulting in an increase in ED presentations of 18.8%.108 A 3-day lag is frequently reported between peak pollen levels and peak asthma admissions.108 Pollen allergy also demonstrates a synergistic relationship with viral infections, as respiratory viral infections are more likely to be associated with severe asthma exacerbations requiring hospitalisation when ambient grass pollen concentrations are high.34,109,110

Pollens are much larger than HDM and mould allergens and are more likely to be filtered out by the upper airway so less penetrates the lower airways.34 This may explain why pollen allergy is more consistently linked to rhinitis and conjunctivitis than to asthma. However, some weather conditions, including thunderstorms, encourage rupture of pollen grains releasing smaller submicronic particles that can penetrate further into the lower airways.34 These may explain the higher incidence of acute asthma exacerbations at these times.108 Pollen allergy may also contribute to worsening asthma control during peak seasons through its impact on AR control.

Children with STRA and seasonal AR with worsening asthma symptoms during pollen season should have personalised management plans that take this into account. Pollens are difficult to avoid so asthma medication may need to be increased pre-season with concomitant treatment of seasonal AR. Omalizumab may be useful in reducing the risk of severe exacerbation in those with STRA.111

## Understanding the relationship between allergy and STRA

The aetiology of STRA in children is complex and likely to be multifactorial, with combined or interacting effects of multiple host and environmental factors. As can be seen above, most studies have focused on a single risk factor for STRA (e.g. mould sensitisation/exposure). Some studies have looked at the interaction between two risk factors (e.g. pollen, mould or HDM sensitisation/exposure and viral respiratory infections). Few studies have attempted to understand how the many factors suspected to contribute to asthma severity interact and quantify the relative importance of each.112 A conceptual model has been developed to understand the pathways through which various risk factors contribute to asthma severity using data from inner-city children receiving optimal guidelines-based asthma treatment.113 This model identified allergy pathways through which increased allergic sensitisation is associated with significantly increased asthma severity through increased allergic inflammation, and subsequently impaired pulmonary physiology and increased rhinitis severity. Had data on allergen exposure been included in the model, the strength of association between allergic sensitisation and asthma severity is likely to have been even stronger. Interestingly, rhinitis severity has a very strong direct effect on asthma severity but not through effects on pulmonary physiology (FEV1 % predicted and FEV1/FVC) as has been suggested previously, so more likely through the impacts of reduced air filtering/conditioning by the upper airways. A second pathway linking environmental tobacco exposure to impaired pulmonary physiology and asthma severity was also identified as important, but other factors including obesity, vitamin D and stress where much less important. These pathways explained 53.4% of the variance in asthma severity in this cohort, highlighting that allergy and environmental tobacco exposure are key determinants of STRA. This model also demonstrates that the relationship between allergy and STRA is complex, with allergic sensitisation mediating asthma severity through downstream effects on airway inflammation, obstruction and rhinitis. Successful interventions that reduce allergic sensitisation, allergen exposure and rhinitis severity in children with STRA may suppress the allergy pathway and reduce asthma severity.

## Allergic sensitisation patterns in STRA phenotypes

Asthma is a heterogeneous disease and even among children with STRA there are large variations in clinical characteristics and responses to treatments.2,114,115 This has led to the idea that there are different asthma phenotypes with shared characteristics and pathophysiological mechanisms. In a study of children with asthma and at least one sensitisation in the Trousseau Asthma Program cohort, two phenotypes of STRA were identified: ‘severe asthma with multiple allergies’ associated with increased inflammatory markers (sIgE and FENO), impaired lung function, co-morbid eczema, allergy to aeroallergens, and the presence of mould in the home; and ‘severe exacerbations with pollen sensitisation’ associated with lower inflammatory markers but increased incidence of hospitalisation for exacerbations of asthma and the highest incidence of food and pollen allergy.22 They also identified two mild asthma phenotypes: ‘mild asthma with HDM monosensitisation’ was the largest group, with the lowest asthma severity and lowest prevalence of eczema and FA; and ‘mild asthma with multiple allergic sensitisations’ with lower IgE and FENO and higher lung function than ‘severe asthma with multiple allergies’ and no association with allergic comorbidities.22 It was suggested the sensitisations in this latter group may represent asymptomatic sensitisations rather than clinically relevant allergy given the lower level of atopy in this group (lower IgE and fewer allergic comorbidities) compared to the SA group.22 So STRA was associated with multiple allergies, including to moulds, and the presence of allergic comorbidities. In the Inner-City Asthma Consortium Asthma Phenotypes in the Inner City (APIC) study, cluster analysis of children with guidelines-managed asthma and rhinitis from nine urban areas of the United States was performed.116 Five asthma phenotypes were identified. Four groups were distinguished by progressively higher asthma severity, degree of allergic sensitisation, allergic inflammation, bronchial hyper-responsiveness, eczema, food allergy and AR. This progressed from a ‘mild asthma and rhinitis, normal lung function and minimally atopic’ group up to the most severe ‘treatment-unresponsive asthma, severely impaired lung function, highly allergic’ group. The fifth group differed significantly from the others as they had highly symptomatic asthma despite high doses of medications but few allergies and minimally abnormal lung function. This group had slightly higher exposure to environmental tobacco smoke, which may have contributed to their asthma severity.

Four other studies attempting to identify asthma phenotypes have used cluster approaches, and each identified a phenotype with characteristics similar to the ‘severe asthma with multiple allergies’ phenotype, either combined with or alongside a ‘severe exacerbations’ phenotype.23,117-119 Phenotypes with predominantly STRA were mostly characterised by increased allergic sensitisation, predominant eosinophilic airway inflammation, , and impaired lung function. However, similar to the APIC study, another phenotype of STRA was identified in several of these studies which involved less allergic sensitisation, fewer allergic co-morbidities, and lower predominance of eosinophilic airway inflammation.24,114,115,118 This highlights the heterogeneity of STRA and suggests that whilst allergy may be an important factor in STRA for many children it is not likely to be driving STRA in all children. It is important to note that the asthma phenotypes in these studies partially overlapped in terms of asthma severity and clinical presentation, with a proportion of children sharing characteristics of more than one group, and no single phenotype corresponded completely with the definitions of STRA proposed in recent guidelines. Potential reasons for the slight differences between phenotypes identified in different studies are differences in study inclusion criteria, and inconsistent inclusion of variables likely to impact on asthma severity.116,120 Cluster analysis may also fail to uncover variables that interact in a complex manner to impact on asthma severity, for example not including exposure to allergens when considering the relationship between sensitisation and asthma severity may mean the link between allergy and STRA phenotypes is less clear.116 Despite this, these phenotyping studies have the potential to improve our understanding of the factors underlying STRA and how they may be modified to improve asthma control.121,122 Longitudinal studies of childhood asthma are needed to confirm the value of these phenotypes in assessment and management of STRA in clinical practice.

## Summary

We found the most evidence for a link between AR and STRA in children. It is possible that the relationship is causal as increasing severity of AR is associated with increasing severity of asthma, there are plausible biological mechanisms for a causal link, and the association remains after adjustment for atopy. An association between eczema and more severe asthma can be seen but this is likely to be due to shared underlying atopic tendencies. There is growing evidence to support a relationship between FA and STRA, with FA seeming to be particularly associated with severe asthma exacerbations in children, but more research is needed to understand the underlying mechanism. The aeroallergen most implicated in STRA is mould, with exposure in sensitised children implicated in severe exacerbations as well as severe persistent asthma as part of the SAFS and ‘severe asthma with multiple allergies’ phenotypes of STRA. There are multiple plausible mechanisms, both allergic and non-allergic, through which mould exposure may drive STRA. Pollen allergy is also associated with acute severe exacerbations of asthma, and likely also contributes to STRA indirectly through AR severity. Pet allergy seems to be associated with STRA in some sensitised children and can even affect those from pet-free homes. Allergies to pests including mouse and cockroach also seem to be an important factor in STRA for some children, particularly in low socio-economic urban areas. HDM allergy has been associated with asthma symptoms but does not seem to be a risk factor for ongoing STRA. However, sensitisation and exposure to any of the three key aero-allergens: HDM, pollens or moulds, increases the risk of severe asthma exacerbations during viral respiratory tract infections.

#### Implications for the clinician

Despite some uncertainty regarding the mechanisms underlying the relationships between STRA and allergy in children, we have seen that exposure to allergens and allergic co-morbidities are intimately linked with asthma morbidity and mortality. A high index of suspicion for the involvement of allergy is needed in cases of acute severe exacerbation of asthma with no identifiable triggers and in children with ongoing STRA. The combination of allergic sensitisation, allergen exposure and viral respiratory tract infection is strongly associated with severe asthma exacerbations (accounting for 69-85% of exacerbations requiring hospitalisation or oral corticosteroids).9,70,100,123 Viral infections cannot presently be prevented, and reduction in allergic sensitisation with immunotherapy is generally contraindicated in severe asthma, hence efforts to reduce allergen exposure are essential. The Community Healthcare for Asthma Management and Prevention of Symptoms (CHAMPS) study has shown that evidence-based asthma interventions tailored to the individual child’s allergic sensitisation and home allergen exposure profile can significantly reduce symptom days in children with moderate-severe asthma compared to a control intervention (difference of days -0.99, p<0.001).124 An approach to identify and manage allergic triggers in STRA is summarised in Box 2.

**Box 2. An approach to identify and manage STRA and allergic triggers** All children with uncontrolled asthma despite treatment with 800µg/day of inhaled budesonide (or equivalent) should be evaluated by a paediatric respiratory specialist and the accuracy of the diagnosis of asthma checked.5,8,14,9,11 Focus should be placed on the following allergy associated issues:

1. Detailed assessment of allergic status:

• A thorough history to establish: previous reactions to allergens (specifically foods, animals/pets/pests, moulds, pollens and HDM), exposures to allergens at home and community (pets, hobbies, visits to homes of others) and any symptoms suggestive of allergic rhinoconjunctivitis.

• Specific IgE testing for likely aeroallergens and potential food allergens by SPT and/or specific IgE tests.14,125,126

5. Management of any co-existing allergies:

• Avoidance of aeroallergens where possible with appropriate education for the family.

• Management of co-existing allergic rhinoconjunctivitis with oral antihistamine, intranasal steroid and/or antihistamine and ocular antihistamine or cromoglycate as required.50

• Management of co-existing food allergy including avoidance advice, personal management plan for allergic reactions and access to self-injectable adrenaline.128-130

• Management of SAFS with avoidance of moulds where possible, including interventions in homes with visible mould, avoidance of mouldy vegetation including stables, and cleaning nebuliser and spacer equipment. Antifungal therapy may need to be considered though evidence for itraconazole and voriconazole in children is weak and may be associated with significant side effects.9,94,131

6. Consider additional therapy to reduce the impact of allergy and optimise asthma control:

• Omalizumab, a monoclonal antibody that binds circulating free IgE, has been successful in improving asthma control in atopic children ≥6 years with STRA.7 However, not all children adequately to Omalizumab.14,16

• Mepolizumab, Reslizumab and Benralizumab are newer monoclonal antibodies targeting interleukin-5, there is currently minimal data on their efficacy for paediatric STRA.141-146

• Subcutaneous or sublingual immunotherapy to symptomatic aero-allergens may reduced asthma severity in children with mild-moderate asthma71,132,133 but safety concerns surrounding the use of immunotherapy in STRA.

#### Future developments

There are several problems to overcome in order to fully understand the role of allergy in driving STRA. Firstly, difficulties interpreting the results of studies investigating the characteristics of children with STRA have arisen from the use of different definitions of SA. The results of studies that have equated problematic severe asthma with STRA, and not identified misdiagnosis and difficult asthma, are likely to differ from those studies looking at true STRA.2,14 This is likely to make identification of STRA phenotypes and their underlying mechanisms less accurate, and means they will be less useful as guides to management of STRA in the clinical setting. Consistent use of problematic severe asthma, difficult asthma, and STRA is vital in order to advance our understanding of STRA and its triggers. Secondly, a limitation of some studies has been assessing sensitisation to allergens based on serology alone and not taking into account clinical reactivity. It is possible that some sensitisations identified by SPT or sIgE reported in the literature are not clinically significant and are therefore of less importance for asthma severity. Studies focusing on clinical allergy are needed but confirming this in large cohort studies is difficult. It is possible that new microarray methods of analysing multiple allergen components will become more widely utilised and may help distinguish clinically significant allergy from biological sensitisations,8,127 and may also shed light on the significance of discordance between sensitisation on SPT and sIgE often detected in clinical practice. Thirdly, many studies investigating risk factors for asthma severity have considered children with STRA and children with mild-moderate asthma as dichotomous groups and fail to account for the heterogeneity within these groups, so will not identify the likely complex multifactorial aetiology of STRA. Phenotyping studies and pathways analyses are helping to address this issue.There is substantial evidence that allergy is an important factor driving STRA and it is likely that STRA phenotypes are, at least in part, differentiated by the type and number of allergic sensitisations and presence and severity of allergic co-morbidities. Improved understanding of these STRA phenotypes will hopefully translate into the clinical setting, where identifying an individual child’s asthma phenotype could help predict their risk of severe exacerbations, identify the allergic co-morbidities and sensitisations that are most important for their asthma control, and allow allergen avoidance and treatment to focus on these triggers.22 For example, children with the ‘severe exacerbations’ phenotype and sensitisation to food or aeroallergens may benefit from Omalizumab.22 Potentially specific immunotherapy may be useful in those with limited clinically important allergens possibly under Omalizumab cover to reduce systemic allergic responses.147

## Conclusions

STRA in children is heterogeneous in relation to allergic sensitisation, lung function, inflammation, and response to treatment, and our incomplete understanding of the underlying mechanisms limits our ability to effectively manage children in this challenging group. Allergic comorbidities particularly AR and FA seem to be important factors driving STRA in some children. Aeroallergens including moulds, pollens, HDM and animal dander have also been implicated in driving STRA in some children, and often act synergistically with viral respiratory infections. It seems that STRA phenotypes in children are differentiated by the type and number of allergic sensitisations and targeting these might lead to improvements in asthma control. Identifying STRA phenotypes and their allergic triggers in clinical practice will be key to further improvement and personalisation of STRA treatment.

## References

1. Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64(6):476-83.

2. Bossley CJ, Fleming L, Ullmann N, et al. Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach. *Journal of Allergy and Clinical Immunology* 2016;138(2):413.

3. De Groot EP, Kreggemeijer WJ, Brand PLP. Getting the basics right resolves most cases of uncontrolled and problematic asthma. *Acta Paediatrica, International Journal of Paediatrics* 2015;104(9):916-21.

4. Bush A, Zar HJ. WHO universal definition of severe asthma. *Current Opinion in Allergy and Clinical Immunology* 2011;11(2):115-21.

5. Bozzetto S, Carraro S, Zanconato S, et al. Severe asthma in childhood: Diagnostic and management challenges. *Current Opinion in Pulmonary Medicine* 2015;21(1):16-21.

6. Kupczyk M, Wenzel S. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? *Journal of Internal Medicine* 2012;272(2):121-32.

7. Bossley C, Suri R. An update on paediatric severe asthma. *Current Allergy and Clinical Immunology* 2013;26(3):114-20.

8. Lodrup Carlsen KC, Hedlin G, Bush A, et al. Assessment of problematic severe asthma in children. *European Respiratory Journal* 2011;37(2):432-40.

9. Bush A, Fleming L, Saglani S. Severe asthma in children. *Respirology* 2017;22(5):886-97.

10. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43(2):343-73.

11. O'Reilly R, Saglani S. Severe asthma: Why do some children not respond to treatment? *Current Pediatric Reviews* 2010;6(2):136-42.

12. Saglani S, Fleming L. How to manage a child with difficult asthma? *Expert Review of Respiratory Medicine* 2016;10(8):873-79.

13. Bel EH, Sousa A, Fleming L, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;66(10):910-7.

14. Bush A, Saglani S. Management of severe asthma in children. *The Lancet* 2010;376(9743):814-25.

15. Ramamurthy MB. Asthma Mimickers: Approach to Differential Diagnosis. *Indian Journal of Pediatrics* 2017:1-6.

16. Konradsen JR, Caffrey Osvald E, Hedlin G. Update on the current methods for the diagnosis and treatment of severe childhood asthma. *Expert Review of Respiratory Medicine* 2015;9(6):769-77.

17. Engelkes M, Janssens HM, De Jongste JC, et al. Medication adherence and the risk of severe asthma exacerbations: A systematic review. *European Respiratory Journal* 2015;45(2):396-407.

18. De Groot EP, Duiverman EJ, Brand PLP. Comorbidities of asthma during childhood: Possibly important, yet poorly studied. *European Respiratory Journal* 2010;36(3):671-78.

19. Vance G, Lloyd K, Scadding G, et al. The 'unified airway': The RCPCH care pathway for children with asthma and/or rhinitis. *Archives of Disease in Childhood* 2011;96(SUPPL. 2):i10-i14.

20. Fitzpatrick AM, Teague WG. Severe asthma in children: Insights from the national heart, lung, and blood institute's severe asthma research program. *Pediatric, Allergy, Immunology, and Pulmonology* 2010;23(2):131-38.

21. Lu KD, Phipatanakul W, Perzanowski MS, et al. Atopy, but not obesity is associated with asthma severity among children with persistent asthma. *Journal of Asthma* 2016;53(10):1033-44.

22. Just J, Saint-Pierre P, Gouvis-Echraghi R, et al. Childhood allergic asthma is not a single phenotype. *Journal of Pediatrics* 2014;164(4):815-20.

23. Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: Confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Journal of Allergy and Clinical Immunology* 2011;127(2):382-89.e13.

24. Denning DW, O'Driscoll BR, Hogaboam CM, et al. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;27(3):615-26.

25. Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe Asthma in Children. *Journal of Allergy and Clinical Immunology: In Practice* 2014;2(5):489-500.

26. Fitzpatrick AM, Baena-Cagnani CE, Bacharier LB. Severe asthma in childhood: Recent advances in phenotyping and pathogenesis. *Current Opinion in Allergy and Clinical Immunology* 2012;12(2):193-201.

27. Arroyave D, Rabito A, Carlson C, et al. Asthma severity, not asthma control, is worse in atopic compared with nonatopic adolescents with asthma. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2016;116(1):18.

28. Just J. Atopy is important in the management of asthma. *Paediatric Respiratory Reviews* 2013;14(2):92-95.

29. Ruokonen M, Kaila M, Haataja R, et al. Allergic rhinitis in school-aged children with asthma - still under-diagnosed and under-treated? A retrospective study in a children's hospital. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2010;21(1 Pt 2):e149-54.

30. de Groot EP, Nijkamp A, Duiverman EJ, et al. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax* 2012;67(7):582-7.

31. Leskela R, Ruokonen M, Korppi M, et al. Association between allergic rhinitis and lung function in school children with asthma. *Current Pediatric Research* 2013;17(1):21-26.

32. Bousquet J, Schunemann HJ, Samolinski B, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs. *Journal of Allergy and Clinical Immunology* 2012;130(5):1049-62.

33. Scadding GK. Optimal management of allergic rhinitis. *Archives of Disease in Childhood* 2015;100(6):576-82.

34. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008\*. *Allergy* 2008;63:8-160.

35. Alsowaidi S, Abdulle A, Bernsen R, et al. Allergic rhinitis and asthma: A large cross-sectional study in the United Arab Emirates. *International Archives of Allergy and Immunology* 2010;153(3):274-79.

36. Deliu M, Belgrave D, Simpson A, et al. Impact of rhinitis on asthma severity in school-age children. *Allergy: European Journal of Allergy and Clinical Immunology* 2014;69(11):1515-21.

37. Higuchi O, Adachi Y, Itazawa T, et al. Rhinitis has an association with asthma in school children. *American Journal of Rhinology and Allergy* 2013;27(1):e22-e25.

38. Hovland V, Riiser A, Mowinckel P, et al. Asthma with allergic comorbidities in adolescence is associated with bronchial responsiveness and airways inflammation. *Pediatric Allergy and Immunology* 2014;25(4):351-59.

39. Sheehan WJ, Phipatanakul W. Difficult-to-control asthma: Epidemiology and its link with environmental factors. *Current Opinion in Allergy and Clinical Immunology* 2015;15(5):397-401.

40. Gobir AA, Mohammed SS, Johnson WBR. Co-existing allergic rhinitis among asthmatics attending the paediatric pulmonology clinic: Implications for control. *African Journal of Respiratory Medicine* 2017;12(2):17-19.

41. Bloom CI, Cullinan P, Quint JK, et al. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018;73(4):313-20.

42. Sasaki M, Yoshida K, Adachi Y, et al. Factors associated with asthma control in children: Findings from a national Web-based survey. *Pediatric Allergy and Immunology* 2014;25(8):804-09.

43. Just J. Determinants of allergic rhinitis in young children with asthma. *PloS one* 2014;9(5):e97236.

44. Braunstahl G-J. The unified immune system: Respiratory tract–nasobronchial interaction mechanisms in allergic airway disease. *Journal of Allergy and Clinical Immunology* 2005;115(1):142-48.

45. Hansen JW, Thomsen SF, Nolte H, et al. Rhinitis: a complication to asthma. *Allergy* 2010;65(7):883-8.

46. Tsilochristou OA, Douladiris N, Makris M, et al. Pediatric allergic rhinitis and asthma: Can the march be halted? *Pediatric Drugs* 2013;15(6):431-40.

47. Motomura C, Odajima H, Taba N, et al. Pale nasal mucosa affects airflow limitations in upper and lower airways in asthmatic children. *Asia Pacific Allergy* 2016;6(4):220-25.

48. Saranz RJ, Lozano A, Lozano NA, et al. Impact of rhinitis on lung function in children and adolescents without asthma. *Allergologia et Immunopathologia* 2016;44(6):556-62.

49. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngology - Head & Neck Surgery* 2015;152(1 Suppl):S1-43.

50. Scadding GK KH, Scadding G. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clin Exp Allergy* 2017;47:856 - 89.

51. von Kobyletzki LB, Bornehag CG, Hasselgren M, et al. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. *BMC Dermatology* 2012;12(11).

52. Saunes M, Oien T, Dotterud CK, et al. Early eczema and the risk of childhood asthma: A prospective, population-based study. *BMC Pediatrics* 2012;12(168).

53. Ballardini N, Kull I, Soderhall C, et al. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: A report from the BAMSE birth cohort. *British Journal of Dermatology* 2013;168(3):588-94.

54. Wang J, Liu AH. Food allergies and asthma. *Current Opinion in Allergy and Clinical Immunology* 2011;11(3):249-54.

55. Naidoo S, Odeyemi I. Does an eczema diagnosis in children under the age of three predict a severe asthma diagnosis: A UK retrospective analysis? *Value in Health* 2013;16 (3):A232.

56. Zicari AM, Indinnimeo L, De Castro G, et al. Food allergy and the development of asthma symptoms. *International Journal of Immunopathology and Pharmacology* 2012;25(3):731-40.

57. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006. *Journal of Allergy and Clinical Immunology* 2010;126(4):798-806.e13.

58. Graif Y, German L, Livne I, et al. Association of food allergy with asthma severity and atopic diseases in Jewish and Arab adolescents. *Acta Paediatrica, International Journal of Paediatrics* 2012;101(10):1083-88.

59. Wang J, Visness CM, Sampson HA. Food allergen sensitization in inner-city children with asthma. *Journal of Allergy and Clinical Immunology* 2005;115(5):1076-80.

60. Roberts G, Patel N, Levi-Schaffer F, et al. Food allergy as a risk factor for life-threatening asthma in childhood: A case-controlled study. *Journal of Allergy and Clinical Immunology* 2003;112(1):168-74.

61. Simpson AB, Glutting J, Yousef E. Food allergy and asthma morbidity in children. *Pediatric Pulmonology* 2007;42(6):489-95.

62. Roberts G, Lack G. Food allergy and asthma—what is the link? *Paediatric Respiratory Reviews* 2003;4(3):205-12.

63. Sargant N, Erlewyn-Lajeunesse M, Benger J. Does anaphylaxis masquerade as asthma in children? *Emergency Medicine Journal* 2014;32(1):83-84.

64. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *Journal of Allergy and Clinical Immunology* 2001;107(1):191-93.

65. Gillman A, Douglass JA. What do asthmatics have to fear from food and additive allergy? *Clinical and Experimental Allergy* 2010;40(9):1295-302.

66. Fernandez Rodriguez C, Bevilacqua E, Fernandez N, et al. Asthma related to Alternaria sensitization: An analysis of skin-test and serum-specific IgE efficiency based on the bronchial provocation test. *Clinical and Experimental Allergy* 2011;41(5):649-56.

67. Sheehan WJ, Phipatanakul W. Indoor allergen exposure and asthma outcomes. *Current Opinion in Pediatrics* 2016;28(6):772-77.

68. Meng J, Barnes CS, Rosenwasser LJ. Identity of the fungal species present in the homes of asthmatic children. *Clinical and Experimental Allergy* 2012;42(10):1448-58.

69. Kaur J, Kabra SK, Lodha R, et al. Association of aeroallergen sensitization with asthma severity and treatment. *Pediatric, Allergy, Immunology, and Pulmonology* 2013;26(4):187-92.

70. Murray CS, Foden P, Sumner H, et al. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *American journal of respiratory and critical care medicine* 2017;196(2):150-58.

71. Eifan AO, Calderon MA, Durham SR. Allergen immunotherapy for house dust mite: Clinical efficacy and immunological mechanisms in allergic rhinitis and asthma. *Expert Opinion on Biological Therapy* 2013;13(11):1543-56.

72. Saglani S, McKenzie SA. Environmental factors relevant to difficult asthma. *Paediatric Respiratory Reviews* 2002;3(3):248-54.

73. Adham TM, Tawfik SA. Dermatophagoides in childhood asthma: Allergy to dermatophagoides associates more severe childhood asthma with a potential role for acaricides. *Saudi Medical Journal* 2012;33(3):292-97.

74. Matsui EC, Sampson HA, Bahnson HT, et al. Allergen-specific IgE as a biomarker of exposure plus sensitization in inner-city adolescents with asthma. *Allergy: European Journal of Allergy and Clinical Immunology* 2010;65(11):1414-22.

75. Li X, Wang X, Lin X, et al. Semi-depot house-dust mite allergen extract for Chinese with allergic rhinitis and asthma. *American journal of rhinology & allergy* 2016;30(3):201-08.

76. Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database of Systematic Reviews* 2008(2).

77. Glasgow NJ, Ponsonby AL, Kemp A, et al. Feather bedding and childhood asthma associated with house dust mite sensitisation: A randomised controlled trial. *Archives of Disease in Childhood* 2011;96(6):541-47.

78. Patelis A, Gunnbjornsdottir M, Malinovschi A, et al. Population-based study of multiplexed IgE sensitization in relation to asthma, exhaled nitric oxide, and bronchial responsiveness. *J Allergy Clin Immunol* 2012;130(2):397-402 e2.

79. Konradsen JR, Nordlund B, Onell A, et al. Severe childhood asthma and allergy to furry animals: refined assessment using molecular-based allergy diagnostics. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2014;25(2):187-92.

80. Downes MJ, Roy A, McGinn TG, et al. Factors associated with furry pet ownership among patients with asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma* 2010;47(7):742-49.

81. Ownby DR. Pet dander and difficult-to-control asthma: The burden of illness. *Allergy & Asthma Proceedings* 2010;31(5):381-4.

82. Perzanowski MS, Ronmark E, James HR, et al. Relevance of specific IgE antibody titer to the prevalence, severity, and persistence of asthma among 19-year-olds in northern Sweden. *J Allergy Clin Immunol* 2016;138(6):1582-90.

83. Nordlund B, Konradsen JR, Kull I, et al. IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobin are markers of bronchial inflammation in severe childhood asthma. *Allergy* 2012;67(5):661-9.

84. Eigenmann PA, Atanaskovic-Markovic M, J OBH, et al. Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. *Pediatr Allergy Immunol* 2013;24(2):195-209.

85. Lødrup Carlsen KC, Roll S, Carlsen KH, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One* 2012;7(8):e43214.

86. Lodge CJ, Lowe AJ, Gurrin LC, et al. Pets at birth do not increase allergic disease in at-risk children. *Clin Exp Allergy* 2012;42(9):1377-85.

87. Grant T, Aloe C, Matsui EC, et al. Mouse Sensitization and Exposure Are Associated with Asthma Severity in Urban Children. *Journal of Allergy and Clinical Immunology: In Practice* 2017;5(4):1008.

88. Sheehan WJ, Baxi SN, Phipatanakul W, et al. Association between allergen exposure in inner-city schools and asthma morbidity among students. *JAMA Pediatrics* 2017;171(1):31-38.

89. Celmeli F, Yavuz ST, Turkkahraman D, et al. Cockroach (Blattella Germanica) Sensitization is Associated with Coexistence of Asthma and Allergic Rhinitis in Childhood. *Pediatric, Allergy, Immunology, and Pulmonology* 2016;29(1):38-43.

90. Rabito FA, Carlson J, Holt EW, et al. Cockroach exposure independent of sensitization status and association with hospitalizations for asthma in inner-city children. *Ann Allergy Asthma Immunol* 2011;106(2):103-9.

91. Rabito FA, He H, Werthmann D, et al. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. *Journal of Allergy and Clinical Immunology* 2017;140(2):565-70.

92. Holme J, Hagerhed-Engman L, Mattsson J, et al. Culturable mold in indoor air and its association with moisture-related problems and asthma and allergy among Swedish children. *Indoor air* 2010;20(4):329-40.

93. Tham R, Dharmage SC, Taylor PE, et al. Outdoor fungi and child asthma health service attendances. *Pediatric Allergy and Immunology* 2014;25(5):439-49.

94. Castanhinha S, Sherburn R, Walker S, et al. Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33. *Journal of Allergy and Clinical Immunology* 2015;136(2):312-22.e7.

95. Gupta A, Singh M, Mathew JL, et al. Correlation between fungal sensitisation in childhood persistent asthma and disease severity. *Mycoses* 2018;61(3):195-200.

96. Bush RK, Prochnau JJ. Alternaria-induced asthma. *Journal of Allergy and Clinical Immunology* 2004;113(2):227-34.

97. Byeon JH, Ri S, Amarsaikhan O, et al. Association between sensitization to mold and impaired pulmonary function in children with asthma. *Allergy, Asthma and Immunology Research* 2017;9(6):509-16.

98. Vicencio AG, Santiago MT, Tsirilakis K, et al. Fungal sensitization in childhood persistent asthma is associated with disease severity. *Pediatric Pulmonology* 2014;49(1):8-14.

99. Lehmann S, Sprunken A, Wagner N, et al. Clinical relevance of IgE-mediated sensitization against the mould Alternaria alternata in children with asthma. *Therapeutic Advances in Respiratory Disease* 2017;11(1):30-39.

100. Tham R, Dharmage SC, Lowe AJ, et al. Associations between outdoor fungal spores and childhood and adolescent asthma hospitalizations. *Journal of Allergy and Clinical Immunology* 2017;139(4):1140.

101. Weinmayr G, Gehring U, Genuneit J, et al. Dampness and moulds in relation to respiratory and allergic symptoms in children: results from Phase Two of the International Study of Asthma and Allergies in Childhood (ISAAC Phase Two). *Clin Exp Allergy* 2013;43(7):762-74.

102. Dannemiller KC, Peccia J, Gent JF, et al. Indoor microbial communities: Influence on asthma severity in atopic and nonatopic children. *Journal of Allergy and Clinical Immunology* 2016;138(1):76.

103. Vicencio AG, Muzumdar H, Tsirilakis K, et al. Severe asthma with fungal sensitization in a child: Response to itraconazole therapy. *Pediatrics* 2010;125(5):e1255-e58.

104. Singh M, Paul N, Singh S, et al. Asthma and Fungus: Role in Allergic Bronchopulmonary Aspergillosis (ABPA) and Other Conditions. *Indian Journal of Pediatrics* 2018:1-6.

105. Kerbelker T, Levin ME. Difficult asthma - 3 case reports. *Current Allergy and Clinical Immunology* 2012;25(3):152-54.

106. Darrow LA, Hess J, Rogers CA, et al. Ambient pollen concentrations and emergency department visits for asthma and wheeze. *Journal of Allergy and Clinical Immunology* 2012;130(3):630-38.e4.

107. Erbas B, Akram M, Dharmage SC, et al. The role of seasonal grass pollen on childhood asthma emergency department presentations. *Clinical & Experimental Allergy* 2012;42(5):799-805.

108. Erbas B, Lambert KA, Parrodi MJ, et al. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: A systematic review and meta-analysis. *Allergy: European Journal of Allergy and Clinical Immunology* 2018.

109. Cook J, Saglani S. Pathogenesis and prevention strategies of severe asthma exacerbations in children. *Current opinion in pulmonary medicine* 2016;22(1):25-31.

110. Erbas B, Dharmage SC, Tang ML, et al. Do human rhinovirus infections and food allergy modify grass pollen-induced asthma hospital admissions in children? *Journal of Allergy & Clinical Immunology* 2015;136(4):1118-20.e2.

111. Brożek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. *Journal of Allergy and Clinical Immunology* 2010;126(3):466-76.

112. Szentpetery SS, Forno E, Han YY, et al. Combined effects of multiple risk factors on asthma in school-aged children. *Respiratory Medicine* 2017;133:16-21.

113. Liu AH, Babineau DC, Krouse RZ, et al. Pathways through which asthma risk factors contribute to asthma severity in inner-city children. *Journal of Allergy and Clinical Immunology* 2016;138(4):1042-50.

114. Fitzpatrick AM. Severe Asthma in Children: Lessons Learned and Future Directions. *Journal of Allergy and Clinical Immunology: In Practice* 2016;4(1):11-19.

115. Just J, Saint Pierre P, Amat F, et al. What lessons can be learned about asthma phenotypes in children from cohort studies? *Pediatric Allergy and Immunology* 2015;26(4):300-05.

116. Zoratti EM, Krouse RZ, Babineau DC, et al. Asthma phenotypes in inner-city children. *Journal of Allergy and Clinical Immunology* 2016;138(4):1016-29.

117. Lang A, Mowinckel P, Sachs-Olsen C, et al. Asthma severity in childhood, untangling clinical phenotypes. *Pediatric Allergy and Immunology* 2010;21(6):945-53.

118. Just J, Gouvis-Echraghi R, Rouve S, et al. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. *European Respiratory Journal* 2012;40(1):55-60.

119. Howrylak JA, Fuhlbrigge AL, Strunk RC, et al. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *J Allergy Clin Immunol* 2014;133(5):1289-300, 300.e1-12.

120. Deliu M, Sperrin M, Yavuz TS, et al. Features of asthma which provide meaningful insights for understanding the disease heterogeneity. *Clinical and Experimental Allergy* 2018;48(1):39-47.

121. Coverstone A, Bacharier LB, Fitzpatrick AM. Severe asthma in school-age children: evaluation and phenotypic advances. *Current allergy and asthma reports* 2015;15(5):20.

122. Ramratnam SK, Bacharier LB, Guilbert TW. Severe Asthma in Children. *Journal of Allergy and Clinical Immunology: In Practice* 2017;5(4):889-98.

123. Puranik S, Forno E, Celedon JC, et al. Predicting severe asthma exacerbations in children. *American Journal of Respiratory and Critical Care Medicine* 2017;195(7):854-59.

124. Kennedy S, Bailey R, Jaffee K, et al. Effectiveness of Evidence-Based Asthma Interventions. *Pediatrics* 2017;139(6).

125. Frith J, Fleming L, Bossley C, et al. The complexities of defining atopy in severe childhood asthma. *Clinical and Experimental Allergy* 2011;41(7):948-53.

126. Schoos AM, Chawes BL, Folsgaard NV, et al. Disagreement between skin prick test and specific IgE in young children. *Allergy* 2015;70(1):41-8.

127. Onell A, Baldracchini F, Mazzoleni G, et al. Allergy testing in children with persistent asthma: comparison of four diagnostic methods. *Allergy: European Journal of Allergy and Clinical Immunology* 2017;72(4):590-97.

128. Stiefel G, Anagnostou K, Boyle RJ, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. *Clin Exp Allergy* 2017;47(6):719-39.

129. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69(8):1026-45.

130. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69(8):1008-25.

131. Castanhinha S, Gupta A, Maglione M, et al. Fungal sensitisation in children with severe therapy resistant asthma. *Thorax* 2011;66:A39-A40.

132. Li H, Yang P, Chen X, et al. A comparative study of sublingual and subcutaneous immunotherapy in mite-sensitive asthmatic children: a single center experience of 90 Chinese patients. *International Journal of Clinical and Experimental Medicine* 2016;9:6743-50.

133. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database of Systematic Reviews* 2015;8:CD011293.

134. Deschildre A, Marguet C, Langlois C, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. *Eur Respir J* 2015;46(3):856-9.

135. Chipps BE, Lanier B, Milgrom H, et al. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. *The Journal of allergy and clinical immunology* 2017;139(5):1431-44.

136. Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: A systematic literature review. *Allergy and asthma proceedings* 2017;38(4):250-63.

137. Pitrez PM, de Souza RG, Roncada C, et al. Impact of omalizumab in children from a middle-income country with severe therapy-resistant asthma: A real-life study. *Pediatric Pulmonology* 2017;52(11):1408-13.

138. Licari A, Castagnoli R, Denicolò C, et al. Omalizumab in Children with Severe Allergic Asthma: The Italian Real-Life Experience. *Curr Respir Med Rev* 2017;13(1):36-42.

139. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136(6):1476-85.

140. Esquivel A, Busse WW, Grindle KG, et al. Effects of Omalizumab on Rhinovirus Infections, Illnesses, and exacerbations of asthma. *American Journal of Respiratory and Critical Care Medicine* 2017;196(8):985-92.

141. Blake K, Raissey H. Mepolizumab: a new class of treatment for adolescents with severe persistent asthma. *Paediatric Allergy, Immunology and Pulmonology.* 2016;29(1):49-52.

142. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta<sub>2</sub>-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *The Lancet* 2016;388(10056):2115-27.

143. Chipps BE, Newbold P, Hirsch I, et al. Benralizumab efficacy by atopy status and serum immunoglobulin E for patients with severe, uncontrolled asthma. *Annals of Allergy, Asthma and Immunology* 2018;120(5):504.

144. Deeks ED, Brusselle G. Reslizumab in Eosinophilic Asthma: A Review. *Drugs* 2017;77(7):777-84.

145. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet* 2016;388(10056):2128-41.

146. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *The Lancet Respiratory Medicine* 2018;6(1):51-64.

147. Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;125(2):383-9.

**Appendix 1:** Literature review search strategy

We performed a literature review using Medline and Embase databases, searching for any relevant articles from 2010 to 2018. Search was last run on 2nd June 2018.

Medline:

1. asthma\*.ti
2. problem\*.ti,ab
3. sever\*.ti,ab
4. difficult\*.ti,ab
5. 2 OR 3 OR 4
6. 1 AND 5
7. exp HYPERSENSITIVITY/
8. hypersensitiv\*.ti,ab
9. allerg\*.ti,ab
10. eczema\*.ti,ab
11. wheez\*.ti,ab
12. DERMATITIS, ATOPIC/ OR ECZEMA/
13. dermatitis.ti,ab
14. rhinitis\*.ti,ab
15. urticaria.ti,ab
16. hayfever\*.ti,ab
17. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. 6 AND 17 [DT 2016-2018] [Languages English] [Human age groups Infant,newborn OR Infant OR Child,preschool OR Child OR Adolescent]

Embase:

1. asthma\*.ti
2. problem\*.tw
3. sever\*.tw
4. difficult\*.tw
5. 2 OR 3 OR 4
6. 1 AND 5
7. exp hypersensitivity/ or exp allergy/
8. hypersensitiv\*.w
9. allerg\*.tw
10. eczema\*.tw
11. wheez\*.tw
12. DERMATITIS, ATOPIC/ OR ECZEMA/
13. dermatitis.tw
14. rhinitis\*.tw
15. urticaria\*.tw
16. hayfever.tw
17. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. 6 AND 17 [DT 2010-2018] [English Language] [Human age groups Infant to one year OR Child unspecified age OR Preschool Child 1 to 6 years OR School Child 7 to 12 years OR Adolescent 13 to 17 years]